

## ULIPRISTAL ACETATE- A NOVEL ORAL EMERGENCY CONTRACEPTIVE: HYPE OR HOPE?

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### ABSTRACT

Unintended pregnancy is a global reproductive health concern. Although emergency contraception is meant to be used after an unprotected intercourse to prevent unwarranted pregnancies, available methods including levonorgestrel 1.5 mg, the currently gold standard EC regimen, is only effective if used as soon as possible after sexual intercourse and before ovulation. Ulipristal acetate (*ellaOne* in the European Union, *ella* in the U.S., HRA Pharma), a novel selective progesterone receptor modulator formulated as a 30-mg emergency contraceptive tablet with similar side effect profiles as levonorgestrel can prevent pregnancy within 120 hours (5 days) after an unprotected intercourse or contraceptive failure on account of its ability to inhibit or delay ovulation. It has been shown to prevent about 60% of expected pregnancies, which is comparable to that provided by levonorgestrel. Two phase 3 prospective, multicenter controlled clinical trials have already demonstrated the safety and effectiveness of ulipristal, according to the USFDA, whose advisory committee has voted unanimously in favor of approving the new drug application in August 2010. However, the findings from a very recent randomized non-inferiority trial comparing the efficacy and safety of ulipristal acetate with levonorgestrel for emergency contraception, has been questioned by scientists and statistical consultants all around the globe based on the premature and misleading conclusions due to lack of sufficient sample size and safety data along with less accessibility and higher cost of the drug. In the light of the above perspectives, ulipristal acetate although provides women and health-care providers with an effective alternative for emergency contraception extended up to 5 days post-unprotected intercourse or contraceptive failure, further long term evidence is warranted before a change in practice should be entertained.

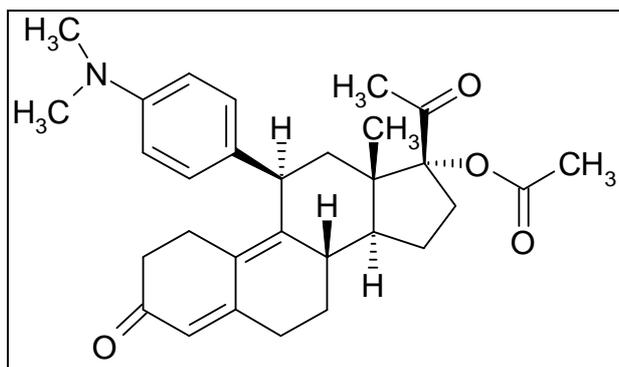
**Keywords:** emergency contraception, ulipristal acetate, levonorgestrel, clinical studies, controversies.

### INTRODUCTION

Emergency contraception (EC), available in more than 140 countries, and in nearly 50 countries without a doctor's prescription, refers to the use of any drug or device following an unprotected intercourse to prevent an unwanted pregnancy.<sup>1</sup> Currently available hormonal methods of emergency contraception prevent at least half of expected pregnancies if taken within 72 hours of unprotected intercourse.<sup>2</sup> The most commonly available regimen involves a single dose, 1.5 mg levonorgestrel pill (taken in a single dose or two 0.75-mg doses 12 hours apart), which is taken up to 72 h of unprotected sexual intercourse to prevent pregnancy, but is more effective the sooner it is taken.<sup>3,4</sup> The first line treatment option with levonorgestrel is facilitated by the ease of access (it can even be purchased without a prescription), ease of administration requiring no third party assistance, its non-invasive nature, an acceptably high level of efficacy, and relatively low cost.<sup>5</sup> However, levonorgestrel's ability to inhibit ovulation is effective only in 50% of menstrual cycles and is most likely to occur at a time when the probability of conception peaks.<sup>6</sup> Furthermore, the efficacy of levonorgestrel declines with time post-unprotected intercourse, and there are only limited evidences of the drug being effective beyond 72 h after sexual intercourse.<sup>4,7,8</sup> The dose dependent efficacy of the synthetic steroid mifepristone, although higher than levonorgestrel, its potential for EC is limited due to social and political reasons for being used as an abortifacient, thereby interfering with and indeed ending implanted

pregnancies, if combined with a prostaglandin analogue.<sup>9</sup> Emergency implantation of a copper bearing intra-uterine device is also effective after 72 h; however, the use is restricted by its availability, high cost, invasive nature and the need for insertion by a skilled and adequately trained health-care professional.<sup>10</sup> Moreover, insertion of the IUD in women with current sexually transmitted infections (STIs) can lead to pelvic infection, which can cause infertility, if untreated.<sup>11</sup> Additionally, many women seeking EC are not seeking a long-acting contraceptive method. In view of these existing limitations with the currently available EC methods, there is an urgent need of an orally active method that is more effective than levonorgestrel and works irrespective of the time of sexual intercourse in the menstrual cycle. Ulipristal acetate (UPA) (*ellaOne* in the European Union, *ella* in the U.S., HRA Pharma), a novel selective progesterone-receptor modulator (SPRM), has therefore, generated surmount interest lately, as a new, longer-lasting and promising alternative in preventing unintended pregnancy for up to 120 hours post-unprotected intercourse or contraceptive failure (figure 1).<sup>12</sup> The aim of this review is to critically evaluate the available evidences to justify the use of ulipristal acetate for emergency contraception after unprotected intercourse, with the purpose to assess whether this new type of second-generation progesterone receptor modulator, represents a new evolutionary step in EC treatment.





**Figure 1:** Chemical structure of ulipristal acetate

#### UPA: Mechanism of action

UPA is a synthetic selective second-generation progesterone receptor modulator (SPRM), derived from 19-norprogesterone, and exert tissue-selective full agonist, antagonist or partial agonist effects at the progesterone receptor.<sup>13</sup> UPA prevents progesterone from binding to its receptor; therefore the gene transcription normally turned on by progesterone is blocked, and the proteins necessary to begin and maintain pregnancy are not synthesized. The primary mode of action is thought to be inhibition or delay of ovulation and a single mid-follicular dose has been shown to suppress growth of lead follicles. When given prior, or in some cases immediately after the luteinising hormone (LH) surge, UPA inhibited 100% of follicular ruptures. It was remarkable to note that even on the day of the LH peak, UPA could delay ovulation for 24–48 h after administration; unlike levonorgestrel.<sup>14</sup>

Early luteal administration of 10–100 mg UPA also results in a reduced endometrial thickness, delayed histological maturation, coupled with alterations in progesterone-dependent markers of implantation, which may subsequently inhibit implantation by rendering the uterus less receptive to the trophoblast.<sup>15</sup>

#### UPA: Pharmacokinetics<sup>13, 16</sup>

##### Absorption

In animal studies, UPA was rapidly and well absorbed from the gut with the maximum plasma concentrations ( $C_{max}$ ) ranging from 1 to 4 hours. Clinical studies involving a single dose administration of the drug in 20 women under fasting conditions showed the  $C_{max}$  of UPA and its active metabolite, monodemethyl-ulipristal acetate to be 176 and 69 ng/ml and were achieved at 0.9 and 1 hour, respectively.

Intake of food although delays absorption, it is not evident whether this is clinically significant; therefore UPA can be taken with or without food.

##### Distribution

UPA is highly bound (96.7–99.5%) to plasma proteins, including high density lipoprotein, alpha-1-acid glycoprotein, and albumin.

#### Metabolism

UPA is rapidly and extensively metabolized in the liver to its pharmacologically active mono-demethylated and di-demethylated metabolites predominantly by cytochrome P450 (CYP3A4). *In vivo* metabolism data in humans are very limited.

#### Excretion

The main excretion route is via the faeces (83.3–44.7%), although biliary excretion was observed in the rats. The terminal half-life of UPA in plasma following a single 30 mg dose is estimated to  $32.4 \pm 6.3$  hours.

#### UPA: Clinical studies

The efficacy and safety studies in support of the EC indication of UPA have been evaluated with different formulations in the clinical trials. Initial research utilized a 50 mg unmicronized tablet, whereas the phase III studies used a 30 mg tablet containing micronized drug particles. Both the formulations are considered to be bioequivalent.<sup>13</sup>

A randomized controlled double-blinded non-inferiority phase II trial (HRA2914-507) in 1549 women aged 18 years and over, compared the efficacy of 50 mg unmicronized UPA with levonorgestrel (0.75 mg twice) used within 72 hours of intercourse and showed that UPA exhibited a trend towards higher efficacy and was indeed statistically non-inferior to levonorgestrel (non-inferiority margin of 2%).<sup>12</sup> Additionally, the results indicated a trend towards higher efficacy of UPA in comparison to levonorgestrel. Of particular significance was the observation that while a sustained efficacy of UPA was demonstrated up to 72 hours after unprotected intercourse, efficacy with LNG decreased over time. Pregnancy rates in the two groups were 0.9% (95% confidence interval 0.2% to 1.6%) and 1.7% (95% CI 0.8% to 2.6%), respectively. In terms of the contraceptive effectiveness, UPA was calculated to have prevented 85% of expected pregnancies compared to 69% in levonorgestrel users ( $p > 0.05$ ).

Another phase II non-inferiority study (HRA2914-508) designed to assess the efficacy and safety of UPA 10 mg micronised vs. 50 mg unmicronised, in 400 women >18 years of age, showed that the micronised formulation was non-significantly inferior to the standard preparation with an estimated 52.38% (95% CI 29.78 – 74.29) of pregnancies prevented compared with 76% (95% CI 52.83 – 91.78).<sup>13</sup> The trial was subsequently used to identify an appropriate dosing formulation of UPA.

A more recent phase III, non-inferiority trial confirmed the efficacy of UPA for EC up to 120 hours of unprotected intercourse, wherein patients were randomized to a single dose of either UPA 30 mg ( $n = 939$ ) or levonorgestrel 1.5 mg ( $n = 954$ ) within 120 hours of coitus.<sup>17</sup> Pregnancy rates were 1.8% (95% CI 1.0% to .0%) for UPA and 2.6% (95% CI 1.7% to 3.9%) for levonorgestrel with an odds ratio (UPA versus

levonorgestrel) of 0.57 (95% CI 0.29 to 1.09). The difference was not statistically significant ( $p > 0.05$ ) and non-inferiority of UPA compared to levonorgestrel was adequately established.

Fine *et al* (2010) again investigated the efficacy and safety of UPA 30 mg in a phase III open label clinical trial with 1533 women over 18 years with regular menstrual cycles presenting between 48-120 hours after unprotected intercourse.<sup>18</sup> The observed pregnancy rate following intake of UPA was 2.1% (95% CI 1.4% to 3.1%), which was statistically inferior to both estimated pregnancy rate of 5.5% and a pre-defined clinical irrelevance threshold. Moreover, the analysis trend did not reveal any increase of pregnancy rate over time up to 120 hours and there were no significant safety issues observed.

To improve the statistical power and provide a better generalisability of results, the databases from the two randomized controlled trials by Crenin *et al* (2006) and Glasier *et al* (2010) were merged in a meta-analysis, wherein, the efficacy of UPA was again compared with levonorgestrel EC (n = 1549 women treated <72 hours after unprotected intercourse plus 1899 women treated <120 hours).<sup>12,17</sup> The results obtained from the analysis of 3445 women indicated that UPA was statistically superior to levonorgestrel for use within 120 hours (OR 0.55, 95% CI 0.32 to 0.93) with reference to the lower pregnancy rate in the UPA group. Furthermore, UPA also exhibited statistical superiority to levonorgestrel for intake within 24 hours of intercourse (n = 1184) with an OR of 0.35 (95% CI 0.11 to 0.93). On the whole, the meta-analysis provides ample evidence that over the 120 hour period UPA is significantly more effective than levonorgestrel at producing a reduced pregnancy rate.

#### **UPA: Adverse effects<sup>13</sup>**

The adverse effects commonly associated with UPA as evident from the phase II and III comparative studies are mainly mild or moderate, short-lasting, self-limiting and similar with both UPA and levonorgestrel. The most frequently observed side effects include lower abdominal pain, nausea, headache and menstrual pain.

#### **UPA: Drug interactions<sup>13</sup>**

Although no specific drug interaction studies have been conducted *in vivo*, UPA is likely to interact with substrates of CYP3A4 (such as rifampicin, phenytoin, phenobarbital, carbamazepine, ritonavir, St. John's wort etc) and with drugs capable of increasing gastric pH (such as proton pump inhibitors, antacids and H<sub>2</sub>-receptor antagonists), which may theoretically reduce plasma concentrations of UPA and hence decrease its efficacy. Concomitant use is therefore not recommended.

Moreover, it may also interfere with the action of progestogen-containing contraceptives since it binds the progesterone receptor with high affinity. In addition, concomitant use of UPA with levonorgestrel EC is theoretically not recommended since an increased ovulation rate may jeopardize contraception.

#### **UPA: Controversies and future directions**

UPA, the first-in-class progesterone receptor modulator, represents a veritable breakthrough in EC technology since it has been demonstrated to be highly efficacious and well-tolerated, thus fulfilling a significant and previously unmet need in this healthcare segment by reducing pregnancy risk up to 5 days after unprotected intercourse by matching the survival time of sperms. However, such reports from the recently concluded randomized single-blind non-inferiority multi-centre trial by Glasier *et al* (2010) projecting UPA as an effective alternative to levonorgestrel for EC has been questioned by scientists and statistical consultants all around the globe in view of the inconsistent methods or statistical analyses used along with the premature and misleading conclusion.<sup>17,19</sup> It has been argued that the trial design drafted and funded by HRA Pharma, the manufacturer of UPA lacks the attributes to prove and justify the efficacy of the drug molecule in preventing pregnancy up to 5 days after unprotected intercourse.

Firstly, the sample size was too small to permit comparisons between UPA and levonorgestrel administered 73–120 h after unprotected intercourse from reaching significance.

Secondly, published reports have acknowledged the fact that an anti-implantation effect cannot be excluded in women receiving UPA 72–120 h after an unprotected intercourse, probably by virtue of a blockade in the effects of progesterone at the level of the endometrial glands and destroying the receptivity of the endometrium. This suggestion has significant practical implications at a time when the experts from the American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG) have begun to accept the fact that levonorgestrel-based emergency contraception does not have abortifacient effects.<sup>20,21</sup>

Finally, high efficacy, easy access and an affordable price are the crucial elements for the success of EC. Hence, a superiority trial must be conducted in order to provide substantial evidence to facilitate UPA's use in current clinical care, since this product is less accessible (need for prescription), more costly (three times the price of levonorgestrel at £16.95 per dose versus £5.37 per dose in Europe), and does not have the same safety data as levonorgestrel.

Thus, to conclude, further long-term safety as well as efficacy related evidence is warranted before a change in EC practice should be entertained, considering the fact that levonorgestrel is the still current choice for EC if administered within 72 h of sexual intercourse and emergency insertion of a copper intrauterine device can also be considered, if feasible. Hence, only the future will be able to show whether UPA will become easily accessible and affordable for women and whether the slightly higher effectiveness compensates the possible disadvantages involved in postponing ovulation, so that despite the issues around health-care service delivery,



UPA will be able to ensure an alternative choice for EC that can be used up to 5 days after unprotected sexual intercourse.

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